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PROGRESS IN AIR POLLUTION MEDICAL  
RESEARCH

Harry Heimann, et al

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**PROGRESS IN AIR POLLUTION MEDICAL RESEARCH**

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**October 15, 1958**

For three years the Air Pollution Medical Branch of the Division of Special Health Services has been working in the increasingly more important but relatively unexplored field of air pollution as it relates specifically to human health. The work began with a search for, and a systematic appraisal of the scattered sources of available knowledge, followed closely by tentative explorations into those portions of the problem holding promise of significant findings. The results of the early activity proved sufficiently successful to help in charting the present course of action which, in turn, appears to be pointing toward those areas which will require emphasis in the future.

This report, intended to highlight only the most broadly meaningful observations and preliminary findings of the Branch, was prepared at the request of the National Advisory Committee, to whose members it was originally presented at a meeting held in Cincinnati on August 28, 1958.

The report is divided into three major parts which conform to the chronological development of the program. Part I treats of the status of knowledge when activities were begun and tells the reasons why the Branch chose to emphasize certain areas of investigation. Part II outlines recent and current activities and explains their significance. Part III summarizes past and present activities and suggests procedures for future action which have evolved from program experience up to this time.

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Discussion Group Reports and Recommendations

National Conference on Air Pollution

- Group A Extent of Air Pollution
- Group B Sources of Air Pollution
- Group C Health Effects
- Group D Economics & Social Effects
- Group E Control Methods & Procedures
- Group F Administrative Aspects

Group A

EXTENT OF AIR POLLUTION

This group's recommendations aimed mainly at increasing our knowledge of the degree to which the Nation's air is polluted.

Major emphasis was placed on the need for more sensitive research instrumentation and for quicker and less expensive field equipment and methods. Other recommendations were:

1. Further consideration should be given to natural air pollutants.
2. Research should be instituted aimed at the development of simple air pollution measurement and warning devices similar to film badges used to check radiation exposure.
3. Less expensive continuous monitoring methods need to be developed.
4. In monitoring operations, peak as well as average values should be determined.
5. The National Air Sampling Network should be continued to study long-term trends. It should be expanded to sample gaseous pollutants. Additional stations producing data comparable to the Network's should be established in larger communities where one Network station is inadequate to determine distribution of pollutants.
6. Knowledge of air pollution could be expanded with a minimum of effort if information on previously unpublished sampling were made available.
7. Existing meteorological data are not being fully used in the solution of community air pollution problems. Communities should be shown how they can apply this data effectively.
8. Specific air pollution meteorological measurements should be devised to supplement current measurements and observations, mainly developed for other purposes.
9. Further research is needed on area sources such as cities and on the natural cleaning of contaminants from the air by washout, rainout, settling and turbulence.
10. A better delineation of air pollution factors responsible for decrease of visibility is needed.
11. Research should be aimed at the development of better and more sensitive tracer techniques, especially those applicable in urban areas.
12. Each community has a limit in the amount of pollutants its atmosphere can safely accept, and there is need for research leading to the establishment of such specific community limits for short and long time periods.
13. Atmospheric contaminants such as CO<sub>2</sub> which may be causing long term climate changes should be monitored on a national basis.
14. There is a definite need for recruitment and training of additional qualified persons to meet the challenge of modern air pollution problems.
15. There is no one best type of organization to support or conduct air pollution research. All available research facilities need to be used in the areas of their greatest competence.

Group B SOURCES OF AIR POLLUTION

Members of Group B recommend that the Public Health Service implement the following program at the earliest possible dates:

1. Intensive development of instrumentation for source analysis.
2. The provision for training of specialized personnel in source studies.
3. The encouragement of communities to assess continually the sources of pollution within their boundaries, with technical assistance from the Public Health Service if requested.
4. The systematic collection, analysis and dissemination of information on emissions from all sources in cooperation with local communities.

It is the consensus of this group that no time should be lost in carrying out these suggestions. The rapid growth of the population and of the national economy and the attendant increase in the quantities of pollution from all sources indicates the need for immediate action.

## GROUP C - HEALTH EFFECTS

Acceleration of research on the medical aspects of air pollution, and the expansion of educational programs, with both activities to be conducted cooperatively by physicians, voluntary and official health agencies were recommended. Specific recommendations for each of these groups included:

For Physicians: Education of private physicians on the hazards of air pollution is of paramount importance and the subject should be taught in both undergraduate and graduate course.

The American Medical Association and other professional organizations should be questioned on whether their programs place enough emphasis on the prevention of diseases caused or aggravated by air pollution and should be encouraged to undertake both research and educational activities. More information on air pollution should also be published by these medical organizations.

Local medical societies should collect information about local air pollution problems and their effect on the people in their communities. This information should be published in local bulletins and discussed at local medical society meetings. Local physicians should also consult with municipal authorities on the legislation needed to cope with their air pollution problems.

Physicians should be well enough informed about the health effects of air pollution to give their patients the facts, thus preventing unwarranted hysteria and at the same time stimulating action against specific or potential air pollution hazards.

### For Voluntary Health Agencies

Paying tribute to the zeal and leadership which voluntary health agencies have always given to problems involving community health, the group recommended that such organizations as the American Cancer Society, the American Heart Association, the National Foundation and the National Tuberculosis Association place more emphasis on air pollution in their programs.

It was suggested that such agencies promote and support research, conduct public education programs, give support to official control programs, and cooperate with medical groups in physician education activities.

### For Government Agencies

Federal support of air pollution control activities should be assured by the extension of the Federal air pollution legislation beyond its current expiration date of 1960, the group agreed. It was recommended that the new legislation put no ceilings on appropriations so that the amount can be considered by Congress annually on the basis of need.

GROUP C - HEALTH EFFECTS (continued)

They also recommended that the Public Health Service invite voluntary health and medical groups to participate in studies of mortality and morbidity and their relationship to air pollution.

Circulation of the proceedings of the National Conference on Air Pollution to physicians and health authorities was advocated.

It was agreed that official agencies at all levels - Federal, State and local - should work more closely with industries, universities, and voluntary health and medical groups, many of which have resources to help deal with the problem that have as yet been untapped.

Although emphasizing the importance of continuing and expanding research education and other activities by all of these groups, the health effects panel nevertheless warned against placing so much stress upon the problem as to create public hysteria which might result in the passage of laws that would cripple industry.

## Group D - SOCIAL AND ECONOMIC ASPECTS

### Education

We recommend a continuing and intensified public information and education program in the following four areas:

education of personnel so that the problems of the future can be met and solved;

education of industry by the dissemination of existing information to industry's obligation for air pollution abatement;

education and assistance for public officials in meeting local problems of air pollution;

education of the general public on its obligations in controlling their own contribution to air pollution problems.

### Research

The following areas need study:

The effect of air pollution upon organisms and materials;

extent and cost of pollution on our economy and society;

extent and cost of air pollution/<sup>control</sup>on our economy and society;

research into administration and legal techniques of air pollution control;

research on sociological implications of air pollution and air pollution abatement;

research and development of new and less costly air pollution control techniques; and

encourage research in by-products and development investigations.

### Action

The Group recommended:

the continuation and expansion of Public Law 159;

the creation of a stronger liaison between Government and the general public and the establishment of a liaison between Government and industry. (With these efforts toward better liaison, we will have an understanding of the meaning of our living together in a cooperative effort);

governmental cooperation with local organizations in the development of programs and effective measures which will further effective and fair air pollution control; and

machinery be set up to promote periodic national meetings for the comparison and evaluation of air pollution control progress.

GROUP E  
CONTROL METHODS AND PROCEDURES

1. The Committee recommends that it is a joint responsibility of government and industry to sponsor and conduct research on air pollution control. It is recognized that industry welcomes government support of research as a means of identifying, defining, and developing approaches to solutions. The responsibility for the solution of specific problems associated with a specific industry or plant lies with that industry.

2. Further research and development should be implemented to expedite controlling emissions from high temperature combustion and metallurgical operations.

3. Further studies must be undertaken to develop economic means for the removal of low concentrations of gaseous pollutants such as oxides of sulfur and nitrogen from combustion gases for application in areas where these may be a problem.

4. We urge that the education and training of engineers in the field of air pollution control should be continued and if possible expanded.

5. Recognition should be accorded to the importance of developing economical survey techniques that can quantitatively define the relative importance of the application of control equipment in a community.

6. Properly designed and engineered control equipment should be incorporated in the initial plant specifications. Codes for guidance in this practice should be developed by voluntary industry groups and engineering societies. Support for this endeavor should be encouraged.

7. In regard to automobile exhaust emissions, the following recommendations are made:

- A. Work on the development of analytical techniques and instrumentation and studies of exhaust gas composition should be continued by both industrial and governmental agencies
- B. Those industries presently engaged in developing exhaust system control devices should continue their work at a vigorous rate.
- C. The automobile industry should continue its study of the maintenance aspects of the automobile exhaust-air pollution problem.

8. Research agencies should continue their program on the health aspects of all air pollutants in order to expedite the development and application of control methods.

9. The study of atmospheric reactions should be continued so that as control methods become available those urban areas affected with an air pollution problem can determine whether or not the application of such control methods will be effective in their particular problem.

## GROUP F - ADMINISTRATIVE ASPECTS

The group agreed that the best way to assess responsibility for air pollution control in a community is to conduct a preliminary study of the problems. In general, however, these responsibilities would fall as follows:

Individual citizens and organizations should reduce to the minimum the air pollution caused by their own activities and should defray the cost of controlling preventable pollution.

Public agencies should collect and dispose of refuse in a manner which will not pollute the air and should set an example to other organizations in observing good air pollution control practices in the operation of their own institutions.

Public agencies should also be responsible for conducting control programs that take into account the topography, meteorology, sources of pollutants and effects that are predominant in the locality.

Official control programs should be supported by public funds plus equitable fees charged for special services rendered to individuals and industries.

Planning and zoning experts should work with air pollution officials in developing data on which can be based standards of air pollution control related to zoning and planning.

Communities should have a balanced air pollution program which includes education, cooperation, regulations and legal enforcement.

Responsibilities of official State agencies should include giving technical assistance to communities in appraising their problem and developing a program.

The State agency should also study air pollution levels throughout the State and assume responsibility for control in areas where local control is not feasible or where local control is needed but has not been established.

Federal activities should include stepped up research on the health effects of air pollution. Federal Air Pollution legislation should be extended indefinitely and there should be no ceilings on appropriations. The latter is recommended because an engineering or medical research break-through may occur at any time, in which case increased funds might be desirable. Moreover, with the rapid increase in industrialization and urbanization increasing the severity of the problem, flexible financing is desirable.

GROUP F - ADMINISTRATIVE ASPECTS (continued)

Control measures, it was agreed should be left to local communities wherever practical, but extended to State and interstate jurisdictions when the problem extends beyond local boundaries. The Federal Government, in the exercise of its jurisdiction over commerce on navigable waters, should delegate responsibility for air pollution control to the States.

The Public Health Service has been concerned with the health aspects of community air pollution for many years. It was not until 1955, however, when Public Law 159 was passed by the 84th Congress, that the subject was accepted as of sufficient importance in itself to merit separate study, rather than as an adjunct to other areas of medical investigation. ~~The new emphasis on the health aspects of community air pollution was assured of proper professional attention and continuity through the establishment of the Air Pollution Medical Program as a constituent part of the Division of Special Health Services in July of 1955.~~

Specifically, the Air Pollution Medical Program was charged with the responsibility of determining whether or not community air pollution modified health among human populations. The first part of this charge involved the problem of definitions. What is meant by community air pollution? What are health effects? What should be the overall goal?

The decision was made that for immediate use air pollutants would be defined as those materials in the community air that were contributed by the acts of man, excluding biological agents and radioactive materials. It was assumed that a community, for our purposes, was an urban aggregation which might well cross political boundaries; it would have a large number of people living together and potentially exposed to generally the same atmospheric air. "Health effects" were defined as those effects which might result in physiological or patho-

logical changes which could be measured by objective techniques. The ultimate goal was seen, even early, to be the definition of those agents in the air which cause deleterious health effects under specified conditions, so that appropriate steps could be taken to prevent or minimize these undesirable effects.

A wide variety of specific items of information were immediately available. For example there was knowledge that within the United States, mortality rates for certain diseases varied from community to community. There was knowledge that eye irritation was present in the Los Angeles Basin and was associated with the local "smog." There was the knowledge that people who had died during the acute air pollution episodes of London, Donora and the Meuse Valley were generally the elderly and especially those who had pre-existing respiratory or cardiac difficulties. From the same episodes and from other data there was evidence that the breathing of irritating material resulted in changes in respiratory physiology. There was evidence that ozone was toxic and that it was present in rather large amounts in the air of such areas as Los Angeles. There was also evidence that sulfur oxides were present in many urban atmospheres and that they could adversely affect human health. Further, information from Great Britain indicated that observed variations in morbidity and mortality from city to city for some specific diseases were similar in pattern to the known or assumed intensity of air pollution.

A large amount of statistical data existed which offered potentially useful information. Use of this material required its reorientation and the exercise of considerable amounts of judgment, since the items had been developed as a result of studies or activities unrelated to air

pollution. A statistical section was organized in our Program and put to work on these data.

Two general courses of action were established. First, studies were designed to define or measure the health status of a community in order to see whether aberrations in health patterns were related to air pollution measures or indexes. These activities were largely either field investigations or "desk" statistical studies. Second, studies were designed to define the biological or health effects of single or multiple known or suspected constituents of air pollution. These were largely laboratory studies. Thus, our Program was divided between epidemiology and laboratory investigations. Certain categorical activities naturally fell into both of these general areas. Our interest and activities in the field of pulmonary physiology and function testing constitute an example of this.

Statistical study was mentioned as an area for initial action by us. We knew that there were large bodies of data in the records of vital statistics units throughout the Country. Some quick and some more detailed examinations of these data from the viewpoint of specific disease were essential to see whether any "good leads" were hidden there. Mortality data provide good, solid quantitative figures, but the specific quality of such data is not as good. For this reason, among others, we needed to examine morbidity records also, where the accuracy of diagnosis was likely to be of much better quality. Organizations such as the Health Insurance Plan of New York City, the Veterans Administration, the Bureau of Old Age and Survivors Insurance, and

others, collect extensive morbidity information. While these mortality and morbidity data were more or less readily available, we found practically no records of air pollution levels to which we might relate them. We had either to develop some kind of index of air pollution that could be applicable to any community or to use the limited data from those very few localities where some air pollution measurements had been made. It was decided to do both. Air pollution indexes have been developed based upon information of populations, industry and fuel consumption for all American metropolitan areas. Specific, although limited, aerometric information is being used in intra-city comparisons. The analyses of these measurements are in process at this time.

Our Program's general responsibility for defining health problems of communities as they may relate to air pollution can be considered as a single, large, complex epidemiological problem to which we are applying, in so far as possible, the methods of epidemiology. This means, simply, the application of specific areas of scientific knowledge to a logical and orderly investigation of a characteristic of a human population. This method originally was developed and applied to the solution of communicable disease problems of man, often occurring as epidemics in the past. In epidemic situations, an identifiable disease is present in unusual numbers in a given population. It is a relatively simple matter to divide the community into those who were well and those who had the disease. When appropriate information has been gathered to describe the differences between these groups, it then becomes possible to investigate how the disease agent was

distributed to the population and how it was propagated. The contribution to the disease spread provided by each of the external factors of the environment could be estimated and even defined in some cases. More recently the general utility and applicability of the epidemiological method, with various modifications, has resulted in its broad use in the study of non-communicable diseases as well, such as mental disorders, home accidents, automobile accidents, heart disease, and even population control.

Many investigations which use this tool, the science of epidemiology, may be tedious and long; but, at least an identifiable disease or condition is present for those studies. Such, unfortunately, is not always the case. Only recently some research laboratories identified infectious agents which were not known to be associated with a disease. Appropriately enough, one such group of organisms was called the "orphan viruses." Surveys have shown that many people carried antibodies for these same viruses. Further investigation revealed the disease.

Those, however, who wish to investigate air pollution health effects are in the unenviable position of having a large group of potential agents and no specific disease. We have some suspicions that non-specific groups of symptoms, which ultimately may constitute air pollution disease, now get thrown in the catchall of "degenerative disease," or constitute conditions assumed to occur "naturally" in the population. Such conditions would include chronic bronchitis, pulmonary emphysema and cardiac deaths.

With such broad and seemingly limitless boundaries to the problem, it was necessary to begin our attack upon a very broad front and be ready to revise and actually to change our directions as information

and leads became available. The pattern of occurrence of chronic bronchitis and lung cancer, on the one hand, and the acute episodes in Donora and London on the other, strongly suggested that there were two different kinds of effect: acute effects producing immediate changes in function, even leading to death, and chronic effects demonstrable only after months or years of exposure, or developing even long after exposure had ceased. The study of these two extremes required different approaches with different methods for identification and quantification of the effects.

## II

Although there is an accumulation of enough random evidence to suggest strongly that air pollution can cause many adverse health effects, reliable medical data of a factual nature are not common. Consequently, for the most part, we have had to start from the very beginning in a search for facts which could withstand careful scrutiny. Considering the diversified nature of air pollution itself, and considering further the many scientific and technical disciplines involved in the study of air and its effects, it becomes clear that our Program has necessarily met with many obstacles in the pursuit of its goal. In spite of these, we believe that we have achieved a creditable degree of success.

The most important known way in which air pollution influences health is that it irritates, and so may possibly damage, membranous

surfaces of the body. Our investigations into the recorded acute air pollution episodes, including one such episode in the study of which one of us (H. H. ) participated, show that the primary effects of such air pollution were on the respiratory tract with secondary, indirect, effects upon the heart. In the Los Angeles area, air pollution appears to have a primary effect upon the eye membranes. These two organ systems, the respiratory tract and the eye, are particularly susceptible to the effects of air pollution for the obvious reason that they are in most immediate contact with the ambient air; and, since this is so, these organ systems will receive special attention in the discussion of our progress to date. However, despite the emphasis on the nature of eye and lung effects, investigations are underway in other areas, such as allergy, cancer, and to a lesser degree, infectious disease.

Working in a field where few guide lines existed, we necessarily placed emphasis on the establishment of effective methods of doing things. Starting from the very beginning, as we were, we had to create and formulate new techniques on how to measure and evaluate the culpability of air pollution components, how to simulate actual air pollution in test situations, how to measure lung airway resistance, how to employ animal experimental "epidemiology," how to establish and use air pollution indexes for expressing relative air pollution levels -- relative in terms of such elusive factors as intensity, duration, and locale. The fact that we already have solved some of these problems and are on our way to solving the remainder is, we feel, an important milestone in the over-all study of the air pollution problem.

One thing we have needed is a lung function testing method suitable for screening large numbers of people. Through some of our own staff efforts and our support of research at Harvard University, there now exists at least one type of testing machine that seems to be suitable for the purpose. It indirectly measures the airway resistance to expiration. At the Occupational Health Field Headquarters of the Public Health Service a group is engaged in complementing the work being done at Harvard. They are considering the problem of how to provide the equipment and personnel suitable for testing a large series of people in their own communities and to determine how such procedures should be applied under conditions of actual field test.

In addition, research being carried on at the University of Pittsburgh and at the University of Cincinnati also is concerned with the effects upon lung function of low concentrations of potential lung irritants. The work accomplished on the development of methods and of actually testing the lung function of large groups of people will play an important role in community health studies, such as the one we are currently carrying on in Nashville, Tennessee. They allow us to test the effect of varying air pollution levels on a vital body function directly related to human comfort and well-being. Used in conjunction with information about various possible environmental influences within a community, this type of objective medical examination can add significantly to the usefulness and reliability of epidemiological investigations as related to air pollution.

✓ We have also, of course, been involved in the classical type

of straightforward epidemiological investigation involving air pollution. In our current program, the first such study that we supported was a re-evaluation of the health of the population of Donora, Pennsylvania, in the light of the 1948 air pollution episode that had occurred in that town. Preliminary data resulting from the re-evaluation indicate that those who lived in Donora at the time of the 1948 episode, and who were adversely affected by the air pollution accumulation at that time, were more likely to have worse health later than did those who lived there during the episode and who apparently were not affected by it at the time. The reason for this difference is not entirely clear at this time.

The epidemiological survey of the Detroit-Windsor area, done as a joint venture by the Governments of Canada and the United States, was begun before our Program was activated. From the data that we have seen thus far, we have been able to deduce only some methodological ideas. We are hoping that more than that will come from the survey when the official reports appear soon,

An important epidemiological investigation is now being carried on in Nashville, Tennessee. Here we are evaluating the health patterns of a people who live in a community where air pollution, when it occurs, is primarily in the form of soft coal smoke. The Nashville study has four broad aspects: 1) A study of mortality by cause and frequency in relation to place and duration of residence; 2) a study from post-mortem examinations of carbonaceous dust accumulations in the lungs, also in relation to place and duration of residence;

- 3) a household morbidity survey to find out about acute and chronic disease in relation to place and duration of residence, and in relation, of course, to current air pollution measurements; and
- 4) a study of the influence of air pollution measurements upon a series of cardio-respiratory disease patients, including a group of persons with bronchial asthma.

Another important approach with relation to our field of interest is the observation of the effects of air-borne irritants upon animals. There often is a very strong correlation between the effects of an environmental factor upon animals and its effect upon humans.

There are three ways, it seems to us, that animals may be used in such investigations. First, wild and domestic animals may be examined for the effects of naturally-occurring pollution. The following are cited as two examples of the many available reports demonstrating this approach. Informed that the health of chickens was adversely affected by air pollution in the Los Angeles area, we supported a field study of this phenomenon. Because the results of this first study were inconclusive, the experiment is now being repeated under well controlled conditions. Research conducted at the University of Southern California has shown that both mouse fertility and the survival rate of newborn mice are reduced by long-continued exposure to the inhalation of low concentrations of synthetic air pollution of the Los Angeles type.

The second way in which we have used animals in our studies is to set up special experimental conditions and to expose the animals

*Dr. C. H. Hart*

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to specific single pollutants or multiple pollutants whose composition is more or less known. We are currently involved in a series of experiments in which this is the broad purpose. Of two such experiments being carried out at Vanderbilt University, the first is to determine exactly where in the respiratory tract the very common air pollutant, sulfur dioxide, impinges to cause its effect. The second involves the lifetime observation of a series of experimental animals (rats) exposed to sulfur dioxide at known low concentrations and another series of animals exposed to bituminous coal smoke.

A third way of using experimental animals is to establish colonies of different species and strains, set them up under adequately controlled conditions, and let them live out their lives in typical, urban areas where they would be exposed to the same atmosphere as that breathed by the human inhabitants. Simultaneously, observations would be made of a group of control animals for which the air is appropriately cleaned to remove the pollutants. We are currently financing such a study at Wayne University and we expect to establish more such animal colonies when time, money, suitable facilities and appropriately trained personnel become available.

We have been very much involved in statistical studies of morbidity and mortality by cause, in relation to air pollution. The work that is being done in this area is divided, broadly, into a study of records of past mortality by cause and past morbidity by cause in relation to environmental factors, including, of course, air pollution. At the same time our statistical unit is looking into recent and current frequency of causes of death and the frequency of illness. In both instances efforts have been concentrated on those clinical entities which we have reason to believe might be causally related to air pollution.

Several months ago we issued the first report to come from our statistical unit, "Comparative Mortality Among 163 Metropolitan Areas of the United States -- 102 Causes of Death." This publication which provides mortality data for many causes, and compares them statistically, has become popular as a source book for public health workers in many fields, in addition to that of air pollution.

The sickness data for the retrospective morbidity studies that we are doing currently were collected from records of the Veterans' Administration files, of veterans receiving disability pensions, and of persons enrolled in the Health Insurance Plan of New York City. From the large amount of data collected from these sources we have thus far been able to make a preliminary estimate of the possible biological significance of only a small portion. The indication is that certain respiratory tract diseases appear with higher frequency in relation to more intense urbanization and, by inference, probably with more intense air pollution.

To study specific diseases and body reactions believed to be associated with air pollution, the nature of the irritant action must be considered. Although irritating substances need not be entirely harmful, they generally are. While ophthalmologists for many years have used irritant materials to stimulate healing of some types of eye ulcers, experimental animals exposed to the inhalation of sub-lethal levels of the respiratory tract irritant, ozone, have developed pulmonary fibrosis of the lung. In both of these reactions, we have examples of the tissue-stimulating properties of certain air pollution components, in the one case being beneficial to the organism and in the other case harmful,

Theoretical considerations based on available data have indicated that, under the peculiar circumstances that may at times exist in the air of the Los Angeles Basin, nitro-olefins may be produced in that atmosphere. However, the actual presence of these compounds has thus far not been demonstrated, probably because of their very labile nature. In spite of this failure, we considered it important that the noxious properties of the nitro-olefins needed study. In a series of investigations conducted at the University of Miami to test their toxic nature, eighteen nitro-olefin compounds thus far tested have proved to be highly damaging to animals, regardless of how they are administered. During the investigations with high dosage, deaths occurred so rapidly that only acute congestion of all vital organs was found. When the specific stress factors of high temperature and humidity were added, deaths of the animals occurred even earlier, a confirmation of general toxicological studies done by others that indicated that biological stress produced in any one of a number of ways, including that involved in physical exertion, intensified the effect of poisons. So far this investigation at the University of Miami confirmed some of the earlier toxicological studies concerning nitro-olefins. Our investigator at the University of Miami is now ready to begin long-term exposures to nitro-olefins in low concentrations -- concentrations that it is believed may occur in community air. We think the results will be significant.

An interesting adventitious observation was made in the early phases of the study of the nitro-olefins. The researchers found that their own eyes were strongly irritated when they handled the compounds or even when they examined the animals that had been treated with those compounds. They, therefore, tried the effect of very low concentrations of the material on themselves, and found that at levels of air

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concentrations near to that which could be present on theoretical grounds in the air of the Los Angeles Basin, they again experienced symptoms of eye irritation. These experiments on eye irritation were repeated by an investigator working in Los Angeles, using a different technique; again, it was observed that eye irritation occurred with exposures to very low air concentrations of the nitro-olefins. The relationship of these observations to the natural phenomenon of eye irritation as it occurs in Los Angeles is, we believe, strongly suggestive.

Other laboratory studies on the mechanism of action of known irritants have been done at the Occupational Health Field Headquarters of the Public Health Service in Cincinnati. Most important were those involving ozone, a gas that has its effect in the deeper parts of the lung. Experimental animals exposed to concentrations lower than those previously considered injurious, suffered fatal pulmonary edema. It was then noted that animals repeatedly exposed to very low, safe concentration levels developed resistance to later exposure to known toxic levels. It is possible that such a protective mechanism may be of importance in protecting man's lungs from injury under natural conditions. Exploration of the nature of this protective action has not been successful, so far. The phenomenon may be related to the fact that, in the test tube at least, ozone reacts with protein to form a new specific antigenic agent. If such a reaction actually occurs between ozone and the surface proteins in the human respiratory tract, it may explain why some resistance to later exposure occurs.

There was one finding -- already mentioned in another context -- that was rather disturbing to us. When animals breathed sub-lethal

concentrations of ozone daily over a period of months, they developed scarring in the lungs. This finding may have great significance to the health of man who may be similarly exposed.

Investigators working in the area of lung function testing have found that the sulfur oxides, gases produced by the burning of the sulfur contained in small but significant amounts in many fossil fuels, cause increased airway resistance. This, it was observed, occurs with air concentrations found on occasion in some urban communities. It has also been demonstrated that a derivative of sulfur dioxide, sulfur trioxide in equal concentration, is even more irritating than the dioxide. Both of these gases are produced when fossil fuels are burned. Finally, it was shown that the effect of the gas, sulfur dioxide, and of certain other irritant gases, is markedly enhanced by the presence of a solid or liquid aerosol which by itself may not be irritating. Aerosols of this type, of course, also commonly appear in the air and especially in that of urban communities. All gases that are irritant do not necessarily have this action enhanced; the nature of the aerosol itself also is of significance in this phenomenon. We are currently studying the possible mechanisms involved in this phenomenon. The belief that the effect of an irritant gas on the lung is enhanced by the simultaneous presence of an aerosol, however, is not accepted by all investigators, but the preponderance of medical opinion is in favor of acceptance. Since it is impossible to conceive of natural air without the presence of an aerosol of some type, the matter may indeed be of significance to human health.

Studying the action of these noxious agents on the body, we were obliged to begin our studies at the primary level. Knowing that the body's response to membrane irritation would involve a series of

protective mechanisms that would mask the effect, we determined that one of the better ways to study membrane irritation would be through isolating cells and cell groups that were being irritated. We are promoting such an activity at Baylor University where the effects of an air pollution mixture upon tissue and cell groups is being investigated. Using a mixture probably containing nitro-olefins as one of the toxicants, positive data available thus far show that such air pollution adversely affects muscle contraction and cell metabolism in special preparations. This work is continuing and has as its ultimate purpose the elucidation of the effect of such air pollutants upon the enzyme systems that are modified to produce these end reactions.

In line with these explorations we approached this same subject through another avenue. We did this by using the tissue culture technique, a tool relatively unexplored for toxicological studies. This technique involves the study of cell preparations, generally of human origin, for changes in growth, reproduction, and metabolism. An authority in the field of tissue culture studies at the University of Nebraska undertook the project for us. Using specific available tissue cultures about which a great deal is known, (fibroblasts, cancerous cervical epithelial cells and liver cells), the investigator showed that very low concentrations of sulfur dioxide stimulate cellular activity; high concentrations of the gas are lethal. The effects of sulfur dioxide, nitrogen dioxide, salts of these acid gases, gasoline, and ozone are continuing under investigation.

Work on the causes and nature of eye irritation has progressed slowly. Research in California has been set up to explore the nature of this phenomenon. Some significant findings have resulted, and it is now generally agreed among authorities that although the eyes of susceptible

persons in Los Angeles become irritated when certain air pollution constituent levels are high, there are no objective changes in the eyes. In addition, the occurrence of eye irritation under experimental conditions is statistically associated with the presence in the air of a group of chemicals that include the nitro-olefins, as already mentioned.

Explorations at the Occupational Health Field Headquarters show that another body system may be affected by irritation from air pollution. While exploring the mechanism involved in the development of pulmonary edema from ozone, which we previously described, it was shown that there was a simultaneous decrease of certain enzymes including alkaline phosphatase in the affected lung tissue. A search was then made for the alkaline phosphatase level in the circulating blood as possibly a more convenient indicator of lung injury. Again, the enzyme level was found to be altered. In the present state of our knowledge we have not been able to extrapolate these findings to the human. But, if we should succeed in doing so, we may be able to detect the degree of lung injury simply by testing a blood sample. This, of course, would constitute a considerable improvement over detection methods now employed.

At the University of Cincinnati, a detailed study of a group of house-ridden cardio-respiratory patients revealed that the diffusion of vital gases across the respiratory membranes into the blood was adversely affected by peak levels of urban air pollution in the Cincinnati area. This may indeed be significant. At the University of Pittsburgh work is going on in an attempt to test the effects of irritant gases upon the lung function of experimental animals in which cardio-respiratory disease has been previously produced artificially.

Interesting and perhaps quite significant in this connection are the findings of a Los Angeles pulmonary physiologist, who, during periods of high air pollution, has placed patients with known lung disease into a special room into which only cleaned air is allowed to enter. After a period of a few hours these people show appreciable improvement in the function of their lungs, and so in their well-being.

In addition to studying the nature of air pollutants, their effects on specific organ systems, and the over-all approach to the evaluation of its effect upon community health, we are also working to observe the relationship of air pollution to specific diseases. At the California State Department of Public Health investigations currently are underway on the effect of air pollution on the natural history of the diffuse clinical syndrome called "chronic bronchitis". Studies of the natural history of chronic bronchitis have been strongly influenced by experience in Great Britain. Air pollution in the British Isles, associated primarily with weather and the industrial use of relatively low-grade solid fuel, has been a subject of considerable interest and concern for a great many years. The acute episode that occurred in the London area in December of 1952, to which some 4,000 deaths were attributed, led to much more intensive medical epidemiological study than there had been before. Some significant concepts stem from these current investigations.

For some time chronic bronchitis has held a high place among the causes of death in Great Britain. As a cause of death it is many times more frequent in that Country than it is in the United States. Without going into the partially successful and partially unsuccessful attempts to consider all the possible variables, and combinations of

variables, that may explain the reasons for the difference, we can certainly say that it is the consensus of enlightened British medical opinion that they do, in fact, have a high frequency of this disease and that its occurrence is very likely associated with the air pollution in their Country. In contradistinction to our predicament, they have identified a disease entity which they can relate to their air pollution. Thus far, we have not done so for the United States.

We have had effective liaison with the British investigators. Efforts currently are in progress to clarify the reasons for the difference between their frequency of chronic bronchitis and ours. There is a prevailing judgment among qualified people that the frequency of this disease in the United States has been increasing in recent years, despite the fact that there still is an appreciable difference between our frequency and Britain's.

Bronchial asthma has also received considerable attention, but the results of several investigations are far from conclusive. A study in Pasadena, California, under the auspices of the California State Department of Health, involved a preliminary survey of the occurrence of asthmatic attacks in relation to certain air pollution variables. The results indicated that there was a doubtful association between certain high air pollution levels and occurrence of asthmatic attacks. This finding surprised us, to say the least. In any case, we are hoping that the observations now being made among asthmatic patients in the Nashville study will be useful in clarifying the matter further.

*New Orleans*

One of the newest aspects of the Air Pollution Medical Program is designed to investigate the size of the health problem caused by air-borne allergens of vegetative and related origins. The study

is in progress now, and the size of the problem has been estimated. Seasonal hay fever, it is estimated, attacks between one and 2-1/2 million people in the United States; bronchial asthma is said to affect from 1/2 to 3-1/2 million persons. We are also obtaining data on the degree of disability that these illnesses cause, and their cost to the Nation in loss of working ability.

The concept which we touched on earlier, to the effect that simple chemical substances may combine with body proteins to form a new substance which may be allergenic, has played an important role in establishing our concern with air-borne allergens or allergen precursors. Such precursors, simple chemical substances, may well be present in polluted air. We discussed briefly how ozone combined with proteins experimentally to result in the formation of a new antigenic agent. The significance of that observation is enhanced by a report received a few years ago from the United States Army in Japan. It appeared that in and about Yokohama some persons of the Army of Occupation and members of their families developed symptoms of bronchial asthma on certain days. This was deemed to be due to material discharged into the air from industrial operations. From the data supplied it is not known just what the specific causative mechanism was. It cannot be ignored, however, that reports of this nature are very rare. A very few reports in the medical literature have directed attention to an allergic response to sulfur dioxide in air; however, the surprising part is that despite the fact that sulfur dioxide is present in the air of so many urban communities, the reports are so rare. We believe that if the matter were looked into more thoroughly, more

reports might be available and we would know more about this aspect of air pollution's effect on health.

Although the field of infectious diseases in the Public Health Service is primarily the concern of the National Institute of Allergy and Infectious Disease and of the Communicable Disease Center, our Program has been somewhat involved with the problem because air pollutants may modify air-borne infectious agents; they also may be active in conditioning exposed human tissue for infection to take place. Early efforts, by others, to study this problem suggested that air-borne chemicals were destructive to some air-borne bacteria and might, therefore, actually reduce the possibility of air-transmitted disease of the respiratory tract. What was not considered in those early studies was the possibility of the alteration by air pollutants of the body membrane surfaces to make them more susceptible to infection than they had been. A few years ago researchers at Johns Hopkins University studied the occurrence of pneumonia in mice exposed to coal smoke and then to pneumococci. The data indicated that pneumonia did not occur more frequently in smoke-exposed mice. However, another investigator, working at the Armour Research Foundation under Air Force auspices, exposed animals to low concentrations of ozone prior to their exposure to air-borne organisms, and found that pneumonia infection was of greater frequency in the exposed animals. We are currently supporting research at the University of California of a study of the influence of ozonized gasoline fumes upon the pneumonia rate in mice, exposed also to a specific virulent pneumococcus.

The growing increase in the frequency of lung cancer throughout the world in recent years has stimulated universal interest. The most

recent data point to cigarette smoke as a major factor. Cigarette smoking notwithstanding, some statistical studies have shown that the cancer rate is higher in urban areas with high air pollution levels than in rural areas with low air pollution levels.

It is generally accepted that the air can carry materials capable of acting as carcinogens. Acceptance of this belief is based in great part on work done with experimental animals. Furthermore, industrial experience has shown that the air inside certain factories contains some carcinogens. It is not difficult, then, to understand that many of these same agents are released into the community air. Furthermore, such well-known experimental carcinogens as benzpyrene have been found in community air; they have also been found in exhaust gas from the internal combustion engine. Research conducted at the University of California at Berkeley has shown that such polycyclic hydrocarbons can be produced by combustion of even some of the simplest straight-chain hydrocarbons under suitable conditions.

Some epidemiologic investigations of the lung cancer problem in Great Britain show that there is an association between urban living, frequency of lung cancer, and the presence in the air of certain polycyclic hydrocarbons already known to be carcinogenic for experimental animals. Preliminary statistical evaluation of certain American mortality data in our own Program bears out the association between air pollution and lung cancer.

Currently in progress -- in the second year of a three year job -- is an investigation of the carcinogenic potential of the particulate matter collected in nine cities in the United States. For these nine

cities there are relatively wide variations in lung cancer frequency. From this biological study of the particulate air-borne material and its fractions, we expect that another bit will be added to our knowledge about air pollution in its relation to the cancer problem.

In considering the relationship of cancer of the lung (or possibly of other organs) to air pollution, some people deny a possible causal connection between the two because, they say, the amount of potential carcinogenic material in the air is too small to be biologically active. Although we can see no immediate resolution to the controversy on this matter that would be acceptable to all, we do keep in mind that there are air-borne materials which may act as adjuvants, enhancing the potential injurious effect of even small amounts of such carcinogenic agents. One of these adjuvant factors is the ability of some air-borne compounds to remove, and thus make active the carcinogenic polycyclic compound sometimes found adherent to an inert particle. Similarly, air-borne irritants because they can slow the rate of removal of potential carcinogens from lung airways, allow longer contact time between the carcinogens and susceptible epithelium. Finally, air-borne irritants cause some denudation of the surface layers of the lining of the air passages, thus exposing the deeper, more susceptible layers to contact with potential carcinogens.

Some investigators have shown that air-borne irritant materials, at least those from cigarette smoke, cause appreciable changes in the epithelial lining of the airways of the human lungs. There are some persons who believe that these changes are directly related to cancer

development. Regardless of whether or not cancer is so related, it is still important to the Air Pollution Program that such irritation causes severe changes in the anatomy and in the functional activity of the human airways. The airways naturally receive primary concern in considering the relation between air pollution and cancer; but other organs also may be involved in such carcinogenesis. A preliminary review of our statistical studies on the frequency of cancer of the esophagus and stomach reveals an association similar to that between air pollution and lung cancer. This finding may be related to some experimental observations wherein it was noted that animals exposed to the inhalation of various dusts showed an appreciable amount of dust in the intestinal tract. This finding also fits, to a certain extent, the occurrence of stomach irritation symptoms that occurred in some of the recorded acute air pollution episodes.

At this point -- at the end of August of 1958 -- then, it appears that we can definitely say that several important indications of significance have appeared in our research projects concerning air pollution and its effects on man. Although further study is required in virtually all fields, it is obvious that we have uncovered some very promising leads.

The findings that we have produced encourage us to continue and expand our investigations.

### III

Carefully analyzing the progress of our Program as it now

exists, we have reached the conclusion that during the next few years we can achieve the best results by concentrating our research efforts on five principal areas. These areas, we believe, represent a logical grouping of all of our varied activities since the inception of the Program. The five areas are as follows:

- I. The relationship of air pollution to variation in the geographic distribution of death and disease, by cause.
- II. The association between air pollution and the functions of the respiratory system.
- III. The association between air pollution and the disease groups of: A) cancer of lung and of other organs, and B) of cardiovascular diseases.
- IV. The effects of specific air pollutants, singly and in combination, in accordance with the varying chemical and physical properties.
- V. The "fringe" areas of air pollution health research.

In regard to the first of these areas -- we have long known that there are important mortality differences among nations, among continents and, to some extent, among so-called races. Only recently, however, have we begun to appreciate the fact that there are important differences in mortality among cities and that most of the differences may occur even among different areas within a city. There is now no doubt that urbanization exerts an effect on health. The higher the degree of urbanization the more prevalent do some diseases become.

We know, of course, that among the many variables that may contribute to these differences are the following: climate, socio-economic status, racial composition, food and water supplies, availability of medical care, and the pattern of customs in medical diagnosis. Despite these other variables, however, we are convinced that air pollution is without doubt an important cause among the many potential causes of geographic variations in mortality and morbidity.

We started late in the field of epidemiology because of the conceptual and operational difficulties involved, the necessity to acquire basic statistical data, and the unfulfilled hope that our initial laboratory investigations would provide information and directions that might simplify the studies of man. Much of the required demographic data has now been acquired.

What are the principal results thus far of our epidemiological studies, preliminary though they may be?

1. There is evidence that the people who were affected by the air pollution episode in Donora in 1948 have more sickness and a higher mortality rate later than their fellow townsmen of similar ages who were not affected.
2. There is evidence that death rates for certain causes increase directly with degrees of urbanization. *presumably AP*  
Specifically, these mortality causes include cancer of the lung, cancer of the stomach and esophagus, arterio-sclerotic heart disease and certain other heart conditions, *and chronic bronchitis.*

*Point*  
3. *There is evidence that changes in the respiratory tract occur as AP increases & as it may be distributed in a city.*

3. Short-term increases in air pollution exposures cause changes in the lung function of persons with chronic cardiorespiratory impairments, and this effect may be delayed for three or four days after the exposure. Exposure to "filtered air" may relieve these symptoms.

Admittedly, these findings are not as definitive or comprehensive as we would like them to be. We feel, however, that they are sufficient to justify the more intensive studies now underway, and those planned for the next few years. This means that we shall continue direct operational support of: 1) statistical analysis of morbidity and mortality data, 2) community surveys, such as those at Nashville and Donora, and 3) morbidity investigations similar to those involving chronic bronchitis and bronchial asthma in California.

The second major area has to do with the effect of air pollution on man's breathing ability. The effects found thus far are essentially those resulting from irritation. The important findings include the following:

1. Irritant gases, such as sulfur dioxide and ozone in amounts not far from those present in community air, have an adverse effect upon man's ability to breathe.
2. Continuous or repeated inhalation of ozone scars the lung tissues of animals.
3. Exposure to ozone disturbs the alkaline phosphatase levels in the body, which may indicate that other changes in enzyme and metabolic activity are occurring.

4. Irritant gases cause pulmonary edema and affect enzyme systems and other physiological mechanisms.
5. Inhalation of some irritant gases mixed with certain aerosols that are usually considered physiologically inert increases the adverse effects of the gases.
6. On the other hand, repeated inhalation of small quantities of ozone, and possibly other gases, appears to result in a significant degree of increased resistance to the acute effects of later-applied heavier exposures.

These findings have resulted in the main from experimental exposures of animals. Their extension to human beings poses obvious difficulties of varying degrees, and in a few instances, efforts of such extension have already begun. We expect to continue to support and carry out the significant leads by the following: 1) Field development of pulmonary function evaluation; 2) continuing research grants in basic and applied pulmonary physiology; 3) direct investigations of effects on animals exposed to irritant pollutants; and 4) research contracts to groups using basic and applied physiological techniques. Although the basic laboratory work involving biochemistry, enzymes, and tissue cultures has shown promise, the findings can not yet be extended to man. Because of the basic nature of this research we believe that it is best supported by the research grant mechanism and we have, therefore, taken steps to convert these studies to that method of support.

Our third major area includes lung cancer, and possibly other cancers, as well as cardiovascular diseases. This brings us to

difficult decisions involving research emphasis and organizational policies.

No one can deny that heart disease and cancer are two of the important disease in this Country today. Together, they account for 54 percent of all deaths. Lung cancer, although accounting for only 1.8 percent of deaths, has been increasing rapidly in recent decades. You are all familiar with the extensive statistical studies relating this increase in lung cancer to cigarette smoking. A similar association has been shown with heart disease mortality, which, although less startling in percentage terms, is even more impressive in total numbers of deaths. What light, if any, have our studies in air pollution thrown upon the causes of these diseases?

1. First, let us consider a finding we discussed under epidemiology, namely, that there is evidence that death rates for certain causes of death increase markedly with urbanization. Specifically, these causes include cancer of the lung, trachea and bronchus, cancer of the stomach and esophagus, arteriosclerotic heart disease and myocardial degeneration. Of interest is the fact that in the case of lung cancer this increase with population density persists even when the degree of cigarette smoking is held constant.

2. Fragmentary evidence of the distribution of cancer mortality within cities appears to be at least partially related to the distribution of air pollution intensity.
3. Certain air pollutants found in our cities are known to be experimentally carcinogenic for animals. Chemical analysis has disclosed many other potential carcinogens in air; these may also be carried by particulate matter deep into the lung.

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Admittedly these are highly important findings which when taken together would justify devoting our entire resources to following them up. However, the total air pollution budget is slightly less than \$4 million, of which, only about 1-1/2 million is available for health studies. In contrast to this we find that the current annual appropriation for heart research is \$46 million, and for cancer is \$75 million. In total, this is a ratio of eighty to one. Consequently, we feel that we can make our most effective contribution in these areas by encouraging those with greater technical and financial resources to undertake epidemiological and laboratory studies oriented toward the stress of the community environment in general, and toward air pollution in particular. An example of this approach is the cooperative arrangements that we worked out with the National Cancer Institute to determine the carcinogenic potential of air pollution particulate samples collected from nine cities by the National Air Sampling Network. We developed the protocol jointly with the National Cancer Institute and the Air Pollution Engineering Program, paid part of the cost of the first year ourselves and made

arrangements to have the National Cancer Institute take over the total cost for the second year. We continue to maintain a close working relationship with the study.

Our fourth concept involves the specific effects of different air pollutants. All our previous experience indicates that the chemical and physical nature of substances are important in determining their biologic effects. We have not devoted much effort to studying the effects of specific substances, largely because our air sampling information indicates that, as an acute problem, the community levels found are too low, and that as a long-term problem it is not possible to isolate effects due to one substance from those due to others. We have, however, promoted research work on the effects of mixtures of pollutants and especially those that generally simulate the type of pollution of Los Angeles. Some of the significant leads that stem from those studies are the following:

1. Certain nitro-olefins are, on theoretical grounds, believed to be present in Los Angeles air pollution and may be among the culprits that cause the unpleasant eye-watering and smarting. In experimental work with synthetically prepared nitro-olefins they have been found to be highly irritating and rapidly fatal to animals in acute exposures. At concentrations which are believed to be possibly extant in Los Angeles air at times, they cause eye irritation in man.
2. There is diminished oxygen uptake and decreased growth of micro-organisms exposed to simulated Los Angeles type of air pollution.

3. The fertility of experimental mice and the survival rate of newborn mice seems to be reduced by the artificial Los Angeles type of air pollution.

The Los Angeles area has made great strides in controlling its original sources of air pollution. The most important remaining uncontrolled source of pollution in Los Angeles is said to be the internal combustion engine. Because of special budgetary considerations we expect to be able to expend a large sum during the next fiscal year on the problem of automobile exhaust gases and their toxicity. These studies will be based in part upon a research facility that is already partially installed. This facility will generate, monitor, and analyze various types of light-irradiated exhaust gases and will then feed them to special exposure chambers which will be designed to study the effects on vegetation, micro-organisms and various species of small experimental animals. The study, or rather the series of studies, will be undertaken by direct operations and by contracts to qualified workers.

Our fifth concept is what we have termed the "fringe" areas of research. This includes those problems that have some relation to the subject of air pollution, but which appear to be of primary concern to researchers who are not in air pollution work. One example is that of the inhalational allergies. This subject is divisible into two problems for us. First, there is the one of the familiar plant pollens causing hay fever and similar reactions. Second, is the question of whether or not chemical air pollutants can cause allergic reactions in some susceptible people. Another example in this "fringe" area is that

involving the effects of swallowing agents present originally as air pollutants. We have found out that many particles inhaled with the air actually reach the gastrointestinal tract. This is of special interest in view of the gastrointestinal effects reported in the study of Donora episode and the association mentioned above regarding stomach cancer. We are not ignoring problems such as these; neither are we devoting any large amount of our resources to them. If our pilot studies indicate the serious possibility of important findings, we are prepared to follow through.

Finally, we would like to point out that what we have described is a blueprint for the near future. These are the things we are doing now or will be doing during the next two or three years. However, we have not neglected consideration of the long-range view. Medical research in air pollution from the long-range aspect, we believe, will be the following:

First, we think we shall some day return to the consideration of effects upon cells and tissues. Methods will some day be developed whereby we will be able to extrapolate the observed effects to intact animals and to human beings. Thus, controlled exposures of isolated cells and of tissues will be a screening device.

Second, we expect that we shall have developed realistic maximal permissible concentrations based on reliable studies, and adaptable to the specific industrial and meteorological conditions of a given city.

Third, we think that the public health engineer and the public health physician will participate much more fully in broad studies of community ecology, in planning and zoning programs and the like. The advantages and disadvantages of alternative proposals may be evaluated, not only in aesthetic and economic terms, but with reference to present and future effects upon the health of the community.

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